Theranostic effect of serial manganese-enhanced magnetic resonance imaging of human embryonic stem cell derived teratoma.

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Authors: J Chung, R Dash, K Kee, J K Barral, H Kosuge, R C Robbins, D Nishimura, Pera R Reijo, P C Yang

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Public Summary:
Although human embryonic stem cells (hESCs) hold therapeutic potential, teratoma formation has deterred clinical applications. Manganese (Mn^{2+}) enters metabolically active cells and can generate high signal intensity on the T1 weighted magnetic resonance imaging. We hypothesized that serial manganese-enhanced MRI could assess hESC-derived teratoma formation and eliminate the teratoma by inducing cytotoxicity through intracellular accumulation of Mn^{2+}. hESCs were transplanted into severe combined immunodeficient mouse (SCID) hindlimbs to form teratoma. Then, these mice were divided into the two groups: chemotherapy group and control group. The chemotherapy group was injected with $MnCl_2$ intraperitoneally three times a week. The control group was given $MnCl_2$ only prior to MRI. Longitudinal evaluation by manganese-enhanced MRI was performed till 8 weeks post-transplant. The chemotherapy group showed significant reduction in the teratoma volume at weeks 6 and 8. Histology revealed increased proportion of dead cells and caspase 3 (apoptosis marker) positive cells in the chemotherapy group. In conclusion, systemic administration of $MnCl_2$ enabled simultaneous monitoring and elimination of hESC-derived teratoma cells by higher intracellular accumulation of Mn^{2+}.

Scientific Abstract:
Although human embryonic stem cell (hESC) hold therapeutic potential, teratoma formation has deterred clinical translation. Manganese ($Mn^{(2+)}$) enters metabolically active cells through voltage-gated calcium channels and subsequently, induces T(1) shortening. We hypothesized that serial manganese-enhanced MRI would have theranostic effect to assess hESC survival, teratoma formation, and hESC-derived teratoma reduction through intracellular accumulation of $Mn^{(2+)}$. Firefly luciferase transduced hESCs (hESC-Lucs) were transplanted into severe combined immunodeficient mouse hindlimbs to form teratoma. The chemotherapy group was injected with $MnCl_{(2)}$ intraperitoneally three times a week. The control group was given $MnCl_{(2)}$ only prior to manganese-enhanced MRI. Longitudinal evaluation by manganese-enhanced MRI and bioluminescence imaging was performed. The chemotherapy group showed significant reduction in the teratoma volume and luciferase activity at weeks 6 and 8. Histology revealed increased proportion of dead cells and caspase 3 positive cells in the chemotherapy group. Systemic administration of $MnCl_{(2)}$ enabled simultaneous monitoring and elimination of hESC-derived teratoma cells by higher intracellular accumulation of $Mn^{(2+)}$. Magn Reson Med, 2011. (c) 2011 Wiley Periodicals, Inc.